NDA 20-369/S-004

Alcon Laboratories, Inc.
do Alcon Research, Ltd.
Attention: Sarah J. Cantrell
Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76 134-2099

JUL 7 2000

Dear Ms. Cantrell:

Please refer to your supplemental new drug application dated January 26, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciloxan® (ciprofloxacin ophthalmic ointment) 0.3% Sterile Ophthalmic Ointment.

We acknowledge receipt of your submissions dated March 23 and June 13, 2000. Your submission of June 13, 2000, constituted a complete response to our March 1, 2000, action letter.

We note that this supplement was submitted as changes being effected. Changes of the kind that you have proposed are not permitted by regulation to be put into effect prior to approval of a supplement. Therefore, this supplement was reviewed under 21 CFR 314.70(b).

This supplement provides for a correction to the Clinical Pharmacology section and revisions to the Adverse Reactions section of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling of the package insert submitted June 13, 2000, with the correction to the corporate signature as agreed to in the June 23, 2000, teleconference between you and Joanne Holmes of this Division.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-369/S-004.” Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MID 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Ciloxan®

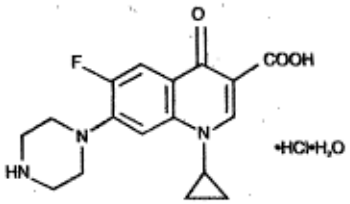
(ciprofloxacin hydrochloride ophthalmic ointment) 0.3% as Base

Sterile Ophthalmic Ointment

DESCRIPTION:

CILOXAN® (ciprofloxacin hydrochloride ophthalmic ointment) Ophthalmic Ointment is a synthetic, sterile, multiple dose, antimicrobial for topical use. Ciprofloxacin is a fluoroquinolone antibacterial. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 385.82. Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$ and its chemical structure is as follows:

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at



the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Each gram ot CILOXAN Ophthalmic Ointment contains:

Active: Ciprofloxacin HCl 3.33 mg equivalent to 3 mg base. lnacttves Mineral Oil, White Petrolatum.

CLINICAL PHARMACOLOGY:

Systemic Absorption: Absorption studies in humans with the ciprofloxacin ointment have not been conducted, however, based on studies with ciprofloxacin solution, 0.3%, mean maximal concentrations are expected to be less than 2.5 ng/mL.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections (SEE iNDICATIONS AND USAGE section).

Aerobic gram-positive microorganisms:

Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus Viridans Group

Aerobic gram-negative microorganisms:

Haemophilus influenzae

The following *in vitro* data are available; **but their clinical significance In ophthalmologic infections is unknown.**

The safety and effectiveness of ciprofloxacin in treating conjunctivitis due to these microorganisms have not been established in adequate and well controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. Ciprofloxacin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 1ug/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens.

Aerobic gram-positive microorganisms:

Bacillus species
Corynebacterium species
Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms:

Acinetobacter calcoaceticus
Enterobacter aerogenes
Escherichia coil
Haemophilus parainfluenzae
Kiebsielle pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcesens

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiplestep mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. Organisms resistant to ciprofloxacin may be susceptible to betalactams or aminogylcosides.

Clinical Studies: In multicenter clinical trials, approximately 75% of the patients with signs and symptoms of bacterial conjunctivitis and positive conjunctival cultures were clinically cured and approximately 80% had presumed pathogens eradicated by the end of treatment (day 7).

INDICATIONS AND USAGE:

CILOXAN Ophthalmic Ointment is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the microorganisms listed below:

Gram-Positive:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus Viridans Group

Gram-Negative:

Haemophilus influenzae

CONTRAINDICATIONS:

A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS:

FOR TOPICAL OPHTHALMIC USE ONLY.
NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose. have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen,

intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

PRECAUTIONS:

General: As with other antibacterial preparations. prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate Therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with The aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction. Ophthalmic ointments may retard corneal healing and cause visual blurring.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information For Patients: Do nof touch tip to any surface as this may contaminate the ointment.

Drug Interactions: Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three in vivo test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to two years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats and mice at doses up to six times the usual daily buman oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg. no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women. CILOXAN® Ophthalmic Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topically applied ciprofloxacin is excreted in human milk. However, it is known That orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when CILOXAN® Ophthalmic Ointment is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of CILOXAN Ophthalmic Ointment 0.3% in pediatric patients below the age of two years have not been established. Although ciprofloxacin and other quinolones may cause arthropathy in immature Beagle dogs after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

ADVERSE REACTIONS:

The following adverse reactions (incidences) were reported in 2% of the patients in clinical studies for CILOXAN Ophthalmic Ointment: discomfort, keratopathy. Other reactions associated with ciprofloxacin therapy occurring in less than 1% of patients included allergic reactions, blurred vision, corneal staining, decreased visual acuity, dry eye, edema, epitheliopathy, eye pain, foreign body sensation, hyperemia, irritation, keratoconjunctivitis, keratopathy, lid erythema, lid margin hyperemia, photophobia, pruritus, and tearing.

Systemic adverse reactions related to ciprofloxacin therapy occurred at an incidence below 1% and included dermatitis, nausea and taste perversion.

DOSAGE AND ADMINISTRATION:

Apply a 1/2" ribbon into the conjunctival sac three times a day on The first two days, then apply a 1/2" ribbon two times a day for The next five days.

How Supplied: Sterile ophthalmic ointment: 3.5 g ophthalmic ointment tube.
3.5 g NDC 0065-0654-35

Storage: Store at 36°F to 77°F (2°C to 25°C).

ANIMAL PHARMACOLOGY:

Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.

Rx Only

U.S. Patent No. 4,670,444

Alcon®
OPHTHALMIC
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA
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